# Review

# Treatment of early diffuse systemic sclerosis skin disease

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**ABSTRACT**

*Diffuse systemic sclerosis carries a high morbidity and mortality. The Prospective Registry of Early Systemic Sclerosis (PRESS), a multicentre incident cohort study of patients with early diffuse cutaneous systemic sclerosis, has the goal of advancing the understanding of disease pathogenesis and identifying novel biomarkers. In this review, PRESS investigators discuss the evidence pertaining to the more commonly used treatments for early diffuse SSc skin disease including methotrexate, mycophenolate, cyclophosphamide, azathioprine, and intravenous immunoglobulin. This review highlights the unmet need for effective treatment in early diffuse SSc as well as its more rigorous study. Nonetheless, the PRESS investigators aim to decrease intra- and inter-institutional variability in prescribing in order to improve the understanding of the clinical course of early diffuse SSc skin disease.*

## Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease characterised pathologically by inflammation, fibrosis and vascular changes resulting in skin fibrosis and internal organ manifestations. Several phenotypes of SSc with varying clinical course and prognosis are recognised.

Prior to serologic subtyping, SSc was traditionally classified based on the extent of skin involvement into diffuse disease manifested by skin thickening proximal to the elbows and knees and limited disease based on absence of proximal skin involvement (1). Additionally, SSc may present with no skin involvement, but with internal organ manifestations along with a SSc-associated antibody, this group is classified under limited SSc and is referred to as scleroderma sine scleroderma. Finally SSc may also present in overlap with features of another connective tissue disease often referred to as overlap or mixed connective tissue disease.

With the advent of advanced immunodiagnostics, numerous SSc-specific autoantibodies have been described and it is becoming clear that many of these autoantibodies predict clinical manifestations including the extent of skin involvement and internal organ manifestations. (2-5). Even with these advances there remains an unmet need to identify biomarkers and prognostic indicators in SSc, both to allow early identification of patients at risk for specific internal organ manifestations and to predict the course of disease complications. Another factor, which impacts longitudinal outcome research in SSc, is that therapeutic interventions are largely based on case-series and historical cohort studies of off-label medication use for FDA-approved drugs (6). There are intra- and inter-institutional variations in prescribing practices, based on patient and prescriber preferences. To date, all available therapeutic options in SSc have only demonstrated limited efficacy. Several randomised clinical trials have investigated immunomodulating agents and failed to show benefit (7-9). These studies may have been negative partially due to undefined underlying SSc pathogenic mechanism, but also because patients were recruited during different phases of disease. The inciting pathologic events in SSc likely occur early in the disease, thus timing of disease-modifying anti-rheumatic drug (DMARD) therapy relative to disease onset may be an important factor, which impacts efficacy.

Our intention is to summarise currently available evidence for DMARDs for SSc skin disease, the intra- and inter-institutional variability in prescribing will be minimised (10). In the long

term, this will help facilitate multicentre collaborations involving longitudinal cohorts of patients with SSc.

The authors of this paper are collaborating on one such multi-centre observational study – the Prospective Registry of Early Systemic Sclerosis (PRESS) that is focusing on developing an incipient cohort of patients with early diffuse SSc with an aim to advance the understanding of disease pathogenesis and identify novel biomarkers. The PRESS study is meant to be complementary to the European Observational Scleroderma Study (ESOS) and United Kingdom Observational SSc study in an effort to better understand early diffuse SSc, which carries a high morbidity and mortality (11). By focusing collaborative efforts on developing a multicentre cohort of patients with early diffuse SSc and standardising biospecimen and data collection across institutions the investigators will generate a well phenotyped data and biospecimen repository for translational studies in this disease. This group of investigators have held face to face meetings on several occasions to review training on standardised physical exams, including nailfold capillaroscopy, and to discuss best practices in regards pharmacologic management of patients with early diffuse SSc (12-14).

In preparation for the meeting, the investigators reviewed pharmacologic options for skin involvement. At this meeting, which occurred in Salt Lake City (SLC) in March 2012, investigators were asked to evaluate their local prescribing practices for skin involvement in SSc and perform a literature review to justify these treatment regimens. In this review, we will summarise the discussions arising from the PRESS SLC meeting, and outline the evidence pertaining to the use of methotrexate, mycophenolate, cyclophosphamide, azathioprine, and intravenous immunoglobulin in SSc for treatment of skin disease. In all studies reviewed disease duration was defined as first non-Raynaud's symptom.

Due to the risk of scleroderma renal crisis (SRC) associated with prednisone use, the PRESS collaborators agreed that when indicated for inflammatory skin changes prednisone would be dosed at 10 mg orally daily or less, unless used for another indication such as myositis. The management of myositis and interstitial lung disease are outside the scope of this review paper, and will be summarised in a later review. Additionally, while an important treatment option for early diffuse SSc patients is enrolment in a clinical trial and for patients who are eligible and willing to participate this may be a preferable early treatment course, these were not reviewed by the investigators and will not be discussed. Targeted small molecule and biologic therapies including anti-TNF-α agents, rituximab, and tyrosine kinase inhibitors including imatinib were discussed at the PRESS SLC meeting, but due to lack of published data were determined to warrant further studies and as such, are not reviewed at present.

Importantly, while this review is not intended as a guideline for prescribing, it is hoped that basing prescribing on the published evidence for methotrexate, mycophenolate, cyclophosphamide, azathioprine and intravenous immunoglobulin will unify the prescription patterns of these agents and reduce confounding that might otherwise impact collaborative longitudinal outcome studies. The intent of this review is only to guide specific PRESS practices for treatment.

**Methotrexate**

Methotrexate (MTX) is a structural analogue of folic acid that competitively inhibits binding of dihydrofolic acid to dihydrofolate reductase thereby blocking the conversion of dihydrofolic acid to folinic acid. Via this pathway MTX inhibits intracellular pathways that are folinic acid dependent including purine and pyrimidine metabolism, amino acid synthesis and polyamine synthesis (15). Additionally MTX increases extracellular dephosphorylation of adenine resulting in increased extracellular adenosine concentrations. *In vivo* MTX exerts its actions via actions on numerous immunomodulatory pathways. It reduces cellular adhesion (16), inhibits clonal proliferation of T and B cells (17), inhibits IL-1β production by mononuclear cells, and inhibits production of proinflammatory cytokines by activated T-cells (18).

The use of MTX for skin and joint involvement in SSc has largely been extrapolated based on its efficacy in rheumatoid arthritis and other autoimmune diseases; however, the impact of MTX on skin progression in early diffuse SSc has been examined in two multicentre, randomised, placebo-controlled, double blind trials (19, 20). Van Den Hoogen *et al*. (20) investigated the role of 15mg intramuscular MTX per week. This study enrolled patients with both diffuse (n=11) and limited scleroderma (n=18) with less than 3 years of skin thickening. They additionally enrolled patients with longer disease duration if there had been progression of skin thickening, persistent digital ulcerations or deterioration in pulmonary function in the preceding 6 months. The primary outcomes included improvement in total skin score or visual analogue scale of well being of greater than or equal to 30% or improvement in diffusion capacity of carbon dioxide (DLCO) of greater than or equal to 15%. At 24 weeks patients demonstrating improvement remained on the same therapy. Non-responders had escalation of MTX dose to 25 mg per week if they were in the treatment arm. Non-responders on placebo were started on MTX 15 mg weekly with escalation to 25mg weekly for the remaining 24 weeks of the study. This study was underpowered and had limitations due to the broad inclusion criteria. However, based on an intention-to-treat analysis there was a 1.2 trend towards improvement in total skin score in the MTX group versus -0.7 trends to worsening in the placebo group ($p$=0.06). This difference was not analysed by the subgroup of diffuse SSc patients.

Pope *et al*. investigated 71 patients with diffuse SSc of <3 years' duration and treated them with either placebo or MTX (15 mg – 17.5 mg orally per week) for 12 months. MTX had a favorable effect on modified Rodnan skin score (mRSS) (mRSS –4.3 in the MTX group *vs*. +1.8 in the placebo group [$p$<0.009]) (19); however, differences in physician global assessment were not significant.

Although low toxicity was reported in both the Pope and Van Den Hoogen studies, neither was powered to demonstrate improvements in internal organ manifestations (21). Re-analysis of the data presented by Pope *et al*. using Bayesian analysis infers that MTX has a high probability of beneficial effects on skin score in SSc (22). Based on these small studies and expert opinion, MTX is recommended by the European League Against Rheumatism (EULAR) and the European Scleroderma Trials and Research Group (EUSTAR) for treatment of skin manifestations of early diffuse SSc (23). A recent consensus guideline study based on responses to electronic surveys sent to members of the Scleroderma Clinical Trials Consortium (SCTC) and the Canadian Scleroderma Research Group (CSRG) found that 62% of scleroderma experts use MTX as first line for treatment of diffuse skin thickening, and 60% use MTX as first line treatment for inflammatory arthritis (10, 24).

Based on these data, if used for skin thickening treatment in the absence of lung disease, the PRESS investigators will prescribe MTX with a dose of 15–25 mg once weekly. The use of oral or subcutaneous dosing will be determined based on gastrointestinal tolerance and skin involvement.

**Mycophenolate**

Mycophenolate is available commercially as mycophenolate mofetil (MMF, Cellcept) and mycophenolate sodium (MS, Myfortic), and is hydrolysed after absorption to the active drug mycophenoloic acid. Mycophenoloic acid reversibly inhibits inosine monophosphate dehydrogenase thus inhibiting conversion of inosine monophosphate to guanosine monophosphate. Since activated lymphocytes are uniquely dependent on purine nucleotide synthesis mycophenolate inhibits lymphocyte proliferation. The use of mycophenolate for treatment of SSc skin thickening stems from the role of these agents in preventing allograft rejection in solid organ transplants and from the experience of using these agents in systemic lupus erythematosus and other autoimmune diseases.

While large randomised trials investigating the use of mycophenolate in SSc are ongoing, several smaller studies have investigated use of mycophenolate for skin and pulmonary involvement in diffuse SSc. In a pilot study patients with early diffuse SSc treated with antithymocyte globulin induction followed by MMF maintenance therapy at a dose of 2g per day showed improvement in skin scores with mean mRSS 28 at baseline dropping to 17 after 12 months of MMF ($p<0.01$) (25). A retrospective analysis of patients with diffuse SSc undergoing open label therapy with MMF (2g per day) compared to a matched group of patients with diffuse SSc receiving other immunosuppression found that the MMF-treated patients had lower frequency of clinically significant pulmonary fibrosis ($p=0.037$) and significantly better 5-year survival both from disease onset ($p=0.027$) and from commencement of therapy ($p=0.012$). There was no significant difference between the two groups in terms of mRSS and change in forced vital capacity (FVC) (26). However, it should be noted that patients in this study were not treatment naïve and more than 68% of the MMF cohort had received other immunosuppressive agents prior to MMF. However, MMF has also been studied in a small cohort of treatment naïve early diffuse SSc patients (27). At 18.2±8.73 months of MMF therapy (median dose 2g per day) the mRSS decreased from 24.56±8.62 to 14.52±10.9 ($p=0.0004$). Skin biopsies from 3 patients demonstrated histopathological improvement and decreased expression of fibrosis-related genes.

Another small open-label study using MMF titrated up to 3g per day for 12 months in 15 diffuse SSc patients with up to 48 months of disease demonstrated significantly improved mRSS in those patients who tolerated the medication for >3 months ($p<0.0001$) (28). MMF has further been examined in diffuse SSc of median disease duration of 12.5 months (IQR 8–23) and compared to historical controls, which had received at relaxin; D-penicillamine, and oral bovine type I collagen (29). In this study, MMF was titrated to 3g per day. A total of 98 patients were included in the primary analysis. The mRSS improvement was seen as early as 3 months and mRSS was significantly lower than historical controls at 12 months ($p<0.001$ D-penicillamine; collagen $p=0.02$).

While all of the currently published studies are limited due to the small numbers of patients, retrospective designs and lack of blinding, recently published consensus guidelines recommend mycophenolate be considered a second line therapy for treatment of skin thickening in SSc (10) and the PRESS investigators plan to adhere to these guidelines. The PRESS investigators will use MMF as an alternative first line agent therapy for rapidly progressive skin disease with titration to maximum of 3g per day in divided doses.

**Cyclophosphamide**

Cyclophosphamide is an alkylating agent used in the treatment of malignancy, vasculitis and lupus nephritis. By cross-linking cellular DNA, cyclophosphamide interferes with cell division and proliferation and reduction in both B- and T-cells is seen.

Two randomised, double blind, placebo-controlled studies have investigated the use of cyclophosphamide in SSc. The Scleroderma Lung Study investigated the use of daily oral cyclophosphamide titrated up to 2mg/kg/day for one year compared to placebo. A small but statistically significant improvement in forced vital capacity (FVC) was seen at 1 year in the cyclophosphamide group (mean absolute difference in FVC% predicted 2.53, 0.28–4.79, $p<0.03$) (30). In patients with diffuse SSc the skin thickness scores also improved by mRSS (31). Monthly intravenous cyclophosphamide has also been investigated in a multicentre study completed in the UK. Patients were treated with prednisolone 20mg every other day and six months of IV cyclophosphamide (600mg/m$^2$/month) followed by oral azathioprine 2.5mg/kg/day to complete a total of 1 year of therapy. While the study did not reach statistical significance the FVC % predicted at 1 year was higher in the treatment than the placebo arm (82.5%

**Table I.** PRESS Treatment for diffuse SSc skin disease.

- Methotrexate with a dose of 15–25 mg once weekly. This will be started orally or subcutaneous.
- Mycophenolate at a dose of 2000–3000 mg daily in divided doses.
- IV cyclophosphamide will be administered at 500 mg/m$^2$ on the first infusion, then increased to 750 mg/m$^2$ or higher for subsequent infusions if patient laboratory parameters and side effect profile will allow for it. MESNA is up to the discretion of the investigator.
- Oral cyclophosphamide will be administered and titrated to a dose of 2 mg/kg/day.
- Azathioprine will be given orally and titrated to a dose of 2 to 3 mg/kg/day and not used if concurrent interstitial lung disease.
- Intravenous immunoglobulin 2 grams/kg infused over 2–5 days

±11.3 compared to 78.0±21.6 $p$=0.08) suggesting that this regimen may stabilise lung function. A study from the Ukraine compared daily oral cyclophosphamide (2mg/kg for 12 months then 1mg/kg) to daily azathioprine (2.5mg/kg for 12 months then 2mg/kg daily). The FVC and DLCO did not change in the cyclophosphamide arm, but showed significant decline in the azathioprine arm again suggesting that cyclophosphamide may stabilise progression of interstitial lung disease. Thus, cyclophosphamide is an important agent to consider for diffuse skin disease if there is concurrent lung disease, but for the purposes of the PRESS investigators is not a preferred agent.

In another study of thirteen patients with early diffuse SSc treated with oral cyclophosphamide (2–2.5 mg/kg/day) and methylprednisolone (30 mg/every other day) for 1 year, the mRSS significantly improved ($p$<0.05) (32). While the effect of the methylprednisolone distinct from cyclophosphamide effect was not evaluated, steroid association with renal crisis is a concern in this patient population.

An alternative cyclophosphamide regimen has been investigated in 6 patients with diffuse SSc at Johns Hopkins Hospital in an open-label, single-site, uncontrolled study. The regimen involves 4 consecutive days of high dose cyclophosphamide 50mg/kg/day (total 200 mg/kg) followed by granulocyte colony-stimulating factor (5 microgram/kg/day). One patient died early in the protocol due to infection. For the remaining five patients the percentage reduction of the mRSS within 1 month of treatment was 60%, 55%, 41%, 31% and 0% (33), and the subject with no initial response showed a 37% improvement by 3 months. This was a high dose immunoablative protocol without stem cell rescue.

As such, when the PRESS investigators administer cyclophosphamide for skin disease it will be used intravenously or orally based on patient and/or centre preference. If administered intravenously, it will be dosed at 500 mg/m$^2$ on the first infusion, then increased to 750 mg/m$^2$ or higher for subsequent infusions if patient laboratory parameters and side effect profile will allow for it. The use of mesna will be up to the discretion of the investigator. Oral cyclophosphamide will be administered and titrated to a dose of 2 mg/kg/day as tolerated.

**Azathioprine**

Azothioprine is a prodrug converted to 6-mercaptopurine (6-MP). 6-MP is then converted to thiopurine nucleotides which reduce de novo synthesis of purine nucleotides and get integrated into the nucleic acids of cells. This results in decreased cellular proliferation and cytotoxicity. The efficacy and toxicity of cyclophosphamide in patients with early diffuse SSc has been compared to azathioprine (AZA) in a randomised, unblinded, 18 months per patient trial (34). In this study, 30 patients were assigned to receive oral cyclophosphamide (2 mg/kg daily for 12 months and then maintained on 1 mg/kg daily) and 30 patients were assigned to receive oral AZA (2.5 mg/kg daily for 12 months and then maintained on 2 mg/kg daily). During the first 6 months of the trial, the patients also received prednisolone, which was started at a dosage of 15 mg daily and tapered to zero by the end of the sixth month. After treatment there was a statistically significant improvement in the mRSS in the cyclophosphamide group, but not in the AZA group. In another study AZA 100 mg daily taken orally has been shown to sustain mRSS score in 13 patients with early diffuse SSc who had completed a year of treatment with low-dose IV pulse cyclophosphamide in a prospective 1-year study (35). Based on these data, azathioprine will not be used if patients have concurrent lung disease, but if used as an alternative agent for skin involvement due to intolerance or unresponsiveness of other agents, PRESS investigators will give AZA orally and titrated to a dose of 2 to 3 mg/kg/day.

**Intravenous immunoglobulin**

Intravenous immunoglobulin (IVIG) contains polyclonal IgG antibodies harvested from pooled human plasma. It is approved by the United States Food and Drug Administration for a variety of immune diseases, and is used off label in many others. The rationale for its use includes its potential immunomodulatory action through neutralisation of autoantibodies, blockage of the Fc receptors on the surface of B-cells and macrophages, and inhibition of inflammatory mediators, however its use in SSc lacks robust evidence at this time (36). Based on animal models (37) and data from dermatomyositis patients it has been postulated that IVIG may down regulate TGFβ (38). Several open label studies have been performed to investigate the role of IVIG in SSc (36). In a two-centre open label study IVIG administered at a dose of 2g/kg over 5 days monthly for 6 months was shown to reduce mRSS (mean decrease 10 ± 5.9, $p$<0.001). This study was limited owing to the small sample size, and inclusion of patients with a wide range of disease duration (4 months to 20 years) (39). Other small studies and case reports also show improvements in skin scores (40) suggesting that IVIG may be a useful therapy for skin involvement in SSc. It perhaps, is most useful in patients with concurrent myositis.

If used by the PRESS investigators, a liquid, pasteurised, 5% concentrated preparation of IVIG will be dosed at 2 g/kg over 2–5 days given monthly for up to six months.

## Conclusions

Management of diffuse SSc is challenging and while some randomised clinical trials are ongoing, to date therapies are of limited efficacy. The relative effectiveness of different therapies in SSc can be compared in an observational way using standardised data entry and outcome measures collected in routine clinical practice, adjusting for confounding by indication to estimate treatment effects (41). To facilitate collaborative longitudinal outcome studies across multiple centres the PRESS investigators have established uniform methodologies for data collection, biospecimen processing and storage. As part of this effort, the PRESS investigators have agreed upon treatment standards based on a review of the current available literature (Table I) for treatment of diffuse SSc skin disease. Focusing therapy based on the available evidence established by consensus review apriori will facilitate longitudinal comparisons of clinical outcomes across different study sites in PRESS. It will furthermore help address the critical challenge of determining best therapy for specific patients based on very limited clinical trial data. International collaboration between PRESS, the UK SSc cohort, and ESOS is anticipated to increase the sample size of this rare disease to allow for statistically powerful results. While the PRESS Registry is not a treatment study, structuring therapeutic options based on available evidence will reduce confounding introduced by collecting data at multiple centres, and will ensure that patients are cared for according to the best available evidence for the duration of their enrolment in the study.

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